Women and Ischemia Syndrome Evaluation (WISE)
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1. Topic and Author

Cost Effectiveness
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2. Where we stand in 2002. Overview/rationale for inclusion of topic.

The cost of diagnosing and treating cardiovascular disease exceeds $329 annually in the US and is a heavy economic burden to most westernized countries (www.americanheart.org). Rising costs of care reflect both changes in the prevalence of disease and dramatic developments in the form of new therapies and technologies for cardiovascular disease. New developments in diagnostic testing contribute to higher resource utilization rates and increasing costs of care. In the US, an estimated 40 million noninvasive cardiac tests are performed, with annualized growth rates as much as 20% (Levin Radiol 2002;222:144-148.).

Economic evaluations, particularly cost effectiveness analysis, combine information on cost with data concerning the accuracy of a screening test, the population at-risk, and the therapeutic benefit to treatment. A comparative analysis of clinical and economic outcome data provides a means to evaluate new technology in relation to existing modalities. Recently, in the US and Europe, a more stringent evaluation of imaging research is consistent with a new standard of evidence-based medicine (Sculpher J Health Serv Res 1997).

3. Current challenges and the most important issues for future research

Defining the Effectiveness of Diagnostic Test for Women

Requisite data for a health economic evaluation include critical information as to the effect of a screening test on patient outcome and alterations in patient management (Berry HTA 1999;3:1-121.). For example, the detection of a high risk imaging abnormality (e.g., coronary calcium score >400) should result in a change in patient management and the initiation of new treatments that ultimately lead to improved survival (He Circulation 2000, Wong Am J Cardiol). The evaluation of a test's ability to risk stratify individuals has been proposed as an alternative to the challenges of assessing diagnostic accuracy (O'Rourke Circulation 2000). For any given test, risk stratification may be used as a method for defining high and low risk cohorts where treatment is allocated to those in greatest need (Califf JACC 1996). Furthermore, the intensity of management is directly proportional to the estimated risk of events, such that, high cost care is allocated to high-risk patients (Califf JACC 1996). Of course, the economic benefit of risk stratification is that, left untreated, many of the high risk individuals would have a cardiac event resulting in more costly care (Wayhs JACC 2002). Furthermore, identification of high-risk patients before the onset of an acute coronary event may offset the significant morbidity and mortality associated with more advanced disease (Sullivan Clin Chim Acta 2002). Conversely, low risk should equate with low cost to the healthcare system.

Measures of test accuracy, such as risk stratification, do not necessarily indicate the likelihood that a test will detect clinically important disease, predict a future event, or most importantly decrease subsequent death or infarction rates. Population-based screening of asymptomatic individuals would be expected to increase the proportion of disease cases detected at an early stage, thus increasing the screening costs of care. One benefit to asymptomatic screening would be if early asymptomatic disease could be treated at a lower cost or with greater efficacy than that noted for the care of symptomatic patients..

The broad range of outcome measures that are applicable to the use of risk stratification include: 1) Intermediate clinical outcomes (e.g., disease detected, cardiac event predicted); 2) Major adverse cardiovascular events (e.g., survival rates); 3) Cumulative effects of test-driven strategy (e.g., life years saved); 4) Patient assessment of a test's value (e.g., quality of life, patient preferences); and 5) Combined quantity and quality of life years (e.g., quality-adjusted life years, healthy-year equivalent, (Berry HTA 1999):

Although multivariable predictive models can be used to describe the interactive nature of both historical and measured risk factors associated with an imaging abnormality and provide an improved method to assess the prognostic value of testing (DeLong Stat Med, Kaplan J Am Stat Soc 1958;53:457-481., Hosmer 1999., Cox. J R Stat Soc B 1972;34:187-220., Concato Ann Intern Med 1993;118:201-10., Goldman Am J Cardiol 1983;51:449-54., Rubin. Ann Intern Med 1997;127:757-63., Lauer J Am Coll Cardiol 1999;34:618-20., Gjorup Br Med J 1986;292:27.), their interpretation can be problematic when considering absolute risks rather than only relative risks.

The supportive rationale for the use of a diagnostic test is that symptoms, established risk factors, physical examination, and functional status measures are often insensitive to disease states, in particular for women (Chambers Neurology 1985, Kuller Stroke 1984, Criqui Circ 1985, Pearson Circulation 2002). For a test to be clinically effective, diagnostic imaging would have to provide new information above and beyond the value of historical (i.e., office visit) and measured risk factors (e.g., cholesterol, glucose) and, possibly, emerging low cost laboratory parameters (e.g., high sensitivity C-reactive protein). This may be calculated by quantifying the amount of added information, often called the test's incremental value. In general, tests that provide more added information would be favored over those that have less content. An exception to this may be that low cost tests that add marginal value may be acceptable to the practitioner and patient. Diagnosis costs can be high when tests add little value (i.e., in low risk individuals, Arnell Am Surg 1996). It is expected that atherosclerotic imaging would have a greater incremental value in intermediate risk individuals (e.g., annualized rate of death or myocardial infarction 0.6%-2.0%) (Greenland, Smith, etc, O'Rourke et al. Circ 2000).

Incremental value may also be measured in terms of differences in patient management or treatment. There has been mixed evidence as to whether diagnostic techniques add value over and above the Framingham risk index (del Sol et al., Stroke 2001, Detrano Circulation 1999). For example, in the Rotterdam Study, carotid intima-media thickness measures in the common carotid artery did not improve the estimation of stroke or myocardial infarction over and above a standard risk factor assessment (receiver operator characteristics (ROC) curve index=0.75 vs. 0.72), although both risk factors and ultrasound measures were equally predictive (ROC curve index=0.72 vs. 0.71).

Using standard epidemiologic methods for the collection of clinical outcomes, consecutive series of individuals are followed for the occurrence of a predetermined clinical event. The effectiveness of screening may be defined as the difference in time between early detection and symptomatic presentation. The number of missed cases can only be estimated if sufficient follow-up is obtained (HTA 1998;2:2). One challenge with imaging is that it is necessary to measure cost and outcome results over a lifetime, or more realistically extrapolate short-term (i.e., 2-3 years) results to a lifetime. For imaging modalities, data on long-term outcomes are exceedingly scarce. Research from observational data sets often include short follow-up time periods that may not reflect the true predictive power of a test in estimating the transition in disease states from subclinical to clinical manifestations of atherosclerotic disease.

Economic evaluations for imaging should be based on the effectiveness of subsequent treatment, accuracy of testing, the cost of testing, and the direct health benefits and resource use resulting from the testing procedure (Goldman JACC 1996). The preferred method to evaluate marginal or incremental differences in clinical and economic outcomes derived from atherosclerotic imaging is to conduct randomized trials comparing different imaging modalities, as previously noted. Historically, the expense associated with this type of evaluation has been beyond the scope of available public and private funding that is allocated to diagnostic testing techniques. When considering testing, the recognition that randomized trials are not practical has led to the frequent use of decision-analytic methods, that is simulations, to try to estimate the cost for some benefit achieved. Principal advantages of modeling are that the analyses may be designed to answer a specific question, drawing available data from multiple sources.

One drawback to the use of a decision model is that data are rarely available in order to answer the specific question and, therefore, numerous assumptions have to be devised using diverse evidence and/or expert opinion. Assumptions can be formally tested through sensitivity analysis but not without interjecting bias or possibly misrepresenting a test's value (Sheldon Healh Econ 1996, Buxton Health Econ 1997). Further extrapolation of evidence on asymptomatic screening to the general population requires the use of additional assumptions about treatment and population-based statistics that may not be available or are biased (Tosteson Circulation 1997;95:24-30., HTA 1997;1:2). As with available data on screening programs in other areas, current data on asymptomatic screening for cardiovascular disease are limited with regard to test cost, induced costs, and the effectiveness and unbiased assessment of screening and treatment of diagnostic tests.

Economic Evaluations in Diagnostic Testing

The aim of economic analyses is to develop an understanding of the cost of alternative health care testing strategies. The calculation of cost effectiveness requires one to specifically describe critical components to an economic analysis including to: a) define the problem; b) differentiate the perspective of the analysis (payer, societal, patient, etc.); c) explicitly state the objective of analysis (guide treatment of patients, help administrators, health policy); d) identify alternatives for comparison; e) explicitly state the outcome of interest: life expectancy, event averted, or functional status, to name a few; f) explicitly state the costs of the alternatives; g) analyze uncertainties and biases (e.g., perform sensitivity analysis); h) explicitly state where there is no evidence or where assumptions have been made; and i) address any ethical issues (Mansley & McKenna, The Lancet 2001;358:1169-1173.).

(Upfront) Test Cost

Unit operating cost of an imaging test can be calculated using fixed and variable labor costs (e.g., supplies, equipment, and labor costs). Unit cost is largely affected by procedural volume and is generally lower when equipment is used to image cardiovascular and non-cardiovascular systems. Imaging modalities that have quantitative scores are generally lower costing than those requiring more technologist or physician labor components. For new technology, there are many unresolved issues that may add cost including laboratory standards or certification, imaging protocols, and evolving equipment (e.g., 4 vs. 16 multisclice CT or 1.5T to 3.0T MR) (Hong Radiol 2002, Schmermund Am J Cardiol 2002 [in press]). Add-on costs such as the use of intravenous contrast agents should be included in test costs. Adjusted (technical and professional) charges may also be used to reflect estimated costs. Additionally, costs should be discounted and adjusted for inflation based upon local or national rates (Smith et al. Int J Technol Assess Health Care 2001;17:236-243., Sheldon J Public Health Med 1992;14:250-256.). Patient waiting times are also an important component of the initial test cost evaluation (Swan Med Decis Making 2000).

Equipment costs vary widely but may be as much as $1 to $4 million for MR, positron emission tomography, and multislice CT scanners. In general, low technology tests (e.g., treadmill exercise or ankle brachial index) are lower cost. Recent innovations in atherosclerotic imaging include the use of multislice (e.g., 16 slice) CT, higher strength (e.g., 3 Tesla) magnets, and MR spectroscopic methods, as such; the precise estimates of cost should be viewed with caution. Many of the new technologies introduced do not have widespread application in the current healthcare marketplace. Therefore, the introduction of new technology will require investment in equipment as well as extensive training of current medical personnel (CoCats).

Induced Cost Models

Total costs should be summed through the entire episode of care, which would include induced downstream resource consumption as well as indirect costs. Indirect costs are those costs which can be thought of as opportunity costs, such as days missed from work (counted as either wages for the patient and/or work not done for the employer) or years of wages not earned by the permanently disabled or deceased patient. Incidental findings would also drive downstream costs of care.

The utility of screening is sensitive to patient preferences that are rarely considered in most cost analyses (Gyrd-Hansen & Sogaard Health Econ 2001;10:617). This is certainly evident in the self-referral patterns to EBT where utilization may be pursued by a patient's willingness to know and pay. Previous reports have noted that patients with evidence of coronary calcium are more likely to consult with their physician, engage in weight loss, decrease dietary fat intake, and initiate new aspirin and cholesterol lowering medications (Wong AJC 1998;78:1220). However, this increase in care seeking behavior may also lead to an increase in worry and lower thresholds for coronary revascularization, thus increasing overall costs of care for this population. Anxiety, inconvenience, and discomfort caused by testing are also indirect costs that are difficult to assess in terms of their monetary value. Travel costs, family labor expenses, out-of-pocket expenses for home monitoring, and deductible rates are indirect costs that should be considered in an economic evaluation. Finally, tests with established quantitative scoring systems generally improve reproducibility thus impacting on downstream costs (Callister Radiol 1998;208:807.).

For imaging, there is a directly proportional relationship between the risk and rate of abnormalities and total costs of care (Shaw Circulation 2002a). That is, individuals with high-risk abnormalities will require numerous procedures beyond the initial test. They are also at greater risk for major adverse cardiac events, including a higher rate of cardiac hospitalizations and coronary revascularization procedures. Thus, future research should focus on the downstream use of medical resources spawned by testing as well as any hospitalizations as a result of a missed diagnosis. In a preliminary report from the HCA healthcare system where detailed direct cost data are available, the inclusion of downstream hospitalizations and major cardiac procedures drastically changed the overall cost estimates (Shaw Circulation 2002a).

Defining Cost Effectiveness of a Diagnostic Test

Cost effectiveness analysis is defined as the amount of resources expended in relation to the clinical outcomes achieved as a means to compare competing tests. The cost-effectiveness ratio, commonly expressed in cost per (quality-adjusted) life year saved may then be compared to other ratios for other medical interventions competing for scarce health care resources (Gold 1996, Office of Technology Assessment, 1980, Doubilet N Engl J Med 1986;314:253-56., Garber J Health Econ 1997;16:1-31., Gold JAMA ~1995, Shaw Imaging in Cardiovascular Disease, eds. G. Pohost, R O'Rourke, P Shah, D Berman, 2000;479-500., Petitti New York, NY: Oxford University Press; 1994., Shaw J Nuc Cardiol 1997; 4:52-60., Mushlin Lancet 2001;358:1353., Goldman JACC 1996). Tests that identify risk and effectively initiate early treatment provide a link to an economic benefit as a result of efficient and effective health care strategies decreasing admissions and overuse of health care services and improving patient outcomes. Tests that are highly accurate have a lower rate of false positive tests (i.e, decreased cost waste due to overuse of cardiac catheterization) and lower rate of false negative tests (i.e., decreased cost waste due to a reduction in hospitalization for unstable angina or myocardial infarction). Cost effectiveness analysis may be defined using the following equation:

$$\text{Incremental CE} = \frac{C_{\text{Test \#1}} - C_{\text{Test \#2}}}{O_{\text{Test \#1}} - O_{\text{Test \#2}}} \qquad \text{(Equation)}$$

Incremental $CE_{\text{Test \#1}}$ is the incremental cost-effectiveness of Test #1 compared to Test #2, C = mean cost, O = mean outcome.

Although others have put forth arguments for other methods of defining economic thresholds, standards for cost effectiveness analysis put forth by the US Public Health Service include measurements in cost per (quality-adjusted) life years saved where thresholds are set at <$50,000 dollars per life year saved (Garber J Health Econ 1997, Gold JAMA 1995). A number of European countries have employed more strict thresholds of ~$20,000 per life year saved.

Cost per life year saved, as a cost effectiveness ratio, has been extensively studied for the evaluation of therapeutic regimens and, in certain cases, for screening programs (Krumholz JACC 2002 [in press]). Given our current knowledge on the effect of imaging on prognosis, available knowledge on the number of patient life years saved would be missing or inadequate more often than not.

Use of Intermediate Outcome Measures

Outcome measures should reflect the clinical decision making process and reflect markers determined during imaging (Hunink Radiol 2002;222:593-594.). Much of our existing cardiac imaging outcomes data do not effectively link posttest decision making in terms of the initiation of medical therapy that alters the outcome of a patient. Cost effectiveness analysis has tremendous limitations when applied to noninvasive testing due to the fact that the link between diagnosis and end results is more often unknown (Mushlin Lancet 2001;358:1353-1355.). Given that much of post-test treatment is uncontrolled, cost effectiveness models would be sensitive to the degree of therapeutic risk reduction (Derdeyn Stroke 1996;27:1944-1950.). For a diagnostic technique, survival is not directly impacted by the test; instead, the results of the test are used to initiate therapy or another procedure. Thus, a diagnostic test has only an indirect benefit on survival, rendering the calculation of cost effectiveness ratios difficult at best but more likely to result in highly biased results.

The rationale for the use of intermediate outcome models is that they reflect the clinical utility of an imaging test. Furthermore, the vast majority of prognostic data for cardiac imaging include 1 to 5 years of follow-up. For individuals followed for the occurrence of ischemic heart disease deaths, the % of deaths observed at 1 year ranges from 0.02% to 9.5% for women and men 35 to 85 years of age. The % of deaths observed at 5-years of follow-up has increased dramatically, especially in those individuals over age 65 years. However, given the limited exposure during 1 to 5 years of follow-up, extrapolation of near term outcome data to changes in life expectancy is challenging. A similar argument can be put forth for the limited amount of economic data that has been collected.

As a solution, some have recommended the use of intermediate outcome measures such as, the cost to identify coronary disease or a cardiac event (Rumberger et al. 1999 JACC). An intermediate outcome model would require fewer assumptions and extrapolations into long-term prognosis but rely upon actual observational data. The major flaw with this type of model is that it varies from accepted standards for cost effectiveness analysis. As based upon current standards, cost effectiveness ratios are defined by cost per life year saved or by a cost utility ratio of cost per quality-adjusted life year saved. This common metric for accepted cost effectiveness models allows for comparison across an array of medical therapeutic regimens and programs. In redefining cost effectiveness methods for diagnostic tests, a new metric and threshold for economic efficiency will have to be defined.

Focused Cost Effectiveness Analysis

A cost-effectiveness ratio can be a dynamic number and is sensitive to multiple demographic variables such as age, gender, the risk of the disease, and the analysis perspective (e.g., society, patient, payer) (Mansley Lancet 2001, Mushlin, Lancet 2001;358:1353). For screening, cost effectiveness ratios often become more favorable beyond a given age (where disease is more prevalent) (Sonnenberg Arch Intern Med 2002;162:163-168., Johnstone, Cancer 2001;15:1075). It is also applicable that the proportional benefit of drug treatment is highly related to the underlying risk in the patient population (Krumholz JACC 2002, Weinstein JGIM 1990;5:S89-S92., Weinstein Ann Rev Pub Health 1985;6:41-63.). These results provide us with a theoretical approach to screening that would detail the fact that imaging tests are generally more cost effective in population subsets for which the test is diagnostically and prognostically accurate. Also, cost effectiveness ratios become more favorable with an increasing risk in a given population series. For example, it is more cost effective to test individuals with an intermediate risk of coronary disease as compared to lower likelihood patients.

Current Evidence on the Cost Effectiveness of Diagnostic Testing in Women

Cost of Evaluating Chest Pain in Women. Half of all women with chest pain referred for coronary angiography do not have obstructive coronary disease as compared with 17% of men (Bell 1995). Comparative data reported from 1980 to 1995 (Bell 1995, Kennedy 1982, Sullivan 1994) and the WISE pilot results indicate that this false positive rate among women has not declined. Cardiac catheterization is currently the most frequently performed procedure for women over age 65 years. One estimate suggests that the excessive rates of normal coronary artery found at catheterization in women results in a cost of over $134 million dollars annually.

The overall diagnostic cost of evaluating chest pain in women approaches $800 million annually (TriCor database, www.americanheart.org). When the cost of noninvasive tests is added, the total diagnostic cost may exceed $1 billion (or

1% of US health care expenditures) (www.americanheart.org). Our current paradigm for the assessment of chest pain symptoms includes identification of patients with obstructive disease for treatment with invasive interventions. Women with a predominance of nonobstructive disease and persistent symptoms do not fit within this current paradigm. Overall, 65% of women found to have normal coronary arteries have persistent or worsening symptoms, test abnormalities, and disability at 5 years after catheterization (Lavey 1971). When patient diagnosis and management is ill defined, significant variability in resource use is expected. For women with normal coronaries, expected annual cost of care is low ($384-$520), with higher costs noted for women with minimally obstructed lesions (<$3,469) (Shaw 1999b). These figures fail to consider medical therapy costs that may add approximately $1,300 to $5,000 to care annually (Weintraub 1995). Thus, a disproportionate share of health care costs in women is driven by symptoms and evidence of ischemia despite the relatively low underlying obstructive coronary disease burden.

Comparative Costs of Various Diagnostic Modalities. Current evidence on the cost of diagnosis for women has been published by several investigators including: 1) the cost of catheterization (Shaw JACC 1999, Shaw J Nuc Cardiol 1999); 2) the cost of nuclear imaging (Shaw JACC 1999, Shaw J Nuc Cardiol 1999); 3) the cost of echocardiography (Kwok 1999, Marwick 1995); and 4) the cost of electron beam computed tomography (EBT) (Rumberger JACC 1999). Table 1 details the upfront and downstream costs of care for women. Although not included, the lowest test cost is for treadmill exercise testing. The highest cost of care ranges from $800 to $5,200 for cardiac catheterization. Despite the added cost, a diagnostic algorithm using one or more WISE tests could achieve substantial cost savings if it effected a reduction in prognostic false positives and/or negatives. For example, a false negative test resulting in admission for a downstream acute infarction could cost as much as $20,000 as compared to less than $1,000 dollars for any of the proposed noninvasive tests.

Table 1. Reported Diagnostic and Follow-up Costs of Care By Noninvasive Tests

Average Cost of Care	**Diagnostic Cost**	**Average Follow-up Cost of Care**
Exercise Echocardiography	$348	$828 until catheterization
Stress SPECT	$650	$1,693 at 2.5 years
EBT	$385	n/a
Cardiac Catheterization	$2,450	$2,740 at 2.5 years

Source: Shaw JACC 1999, Marwick JACC 1995, Rumberger JACC 1999, Kwok Am J Cardiol 1999

Cost Effectiveness. Cost effectiveness of testing has been defined as *the amount of resources required in order to achieve desired patient outcomes* (Goldman JACC 1996). It combines information derived from prognostic models with the amount of resources required to make meaningful outcome assessments. The general principle of high-risk cost effectiveness dictates that as the test becomes more clinically effective (i.e., substantial added value), it will also become more cost effective. Previous data demonstrates that a targeted approach to cost effectiveness or high-risk cost effectiveness models may more accurately mirror the estimation of prognosis (Goldman JACC 1996, Weintraub Circulation 1999). According to these analyses, optimizing prognostic estimates produces distinct risk subsets that may benefit from tailored therapeutic risk reduction. Hence the accurate identification of risk reduces results in effective stratification of cost subsets and the possibility of targeting therapies known to effect outcome benefit (Shaw and Papatheofanis 1999, Weintraub

Circulation 1999).

Cost Savings Models. Resource efficiency may be defined as a minimal set of procedures that may be employed in order to achieve a given outcome estimate. This may also be termed cost minimization or savings. A recent example of this analysis in women with stable chest pain was published by Shaw et al. (1999 J Nucl Cardiol) where the costs encumbered prior to a cardiac death was evaluated using a cost Cox proportional hazards model. This is defined as the lowest cost strategy given similar outcomes between the test comparisons of interest (Berman JACC 1995, Goldman JACC 1996, Hachamovitch Circulation 1998, Marwick 1995, Shaw JNC 1997, Shaw JNC 1999). When multiple tests are performed, it is possible to identify the most accurate tests (in terms of risk stratification) while considering the property of selective resource use (i.e., constrained use of higher cost testing) (Berman JACC 1995, Goldman JACC 1996, Hachamovitch Circulation 1998, Marwick JACC 1995, Shaw JNC 1997, Shaw JNC 1999). Cost savings may be variable by important patient subsets (Berman JACC 1995). For example, documented savings may be enhanced when sequential testing, including cardiac catheterization, is performed on women with ischemia as compared to those without test abnormalities. There may also be important female covariates that enhance identification of risk and result in economic efficiency (Berman JACC 1995). When important patient subsets have been identified, as much as 40% cost savings was achieved through selective resource use (Berman JACC 1995, Shaw JNC 1999).

Cost of Diagnostic Algorithms Using Test Combinations. An increasing body of evidence suggests that part of the defining of quality health care requires delineation of cost waste due to inaccurate diagnostic techniques. Hence the true economic value of a patient management algorithm may only be defined after a highly accurate prognostic estimate is established. The WISE study was designed to develop a diagnostic algorithm for women, and in the current proposal to expand this strategy in economic terms to a disease management strategy. The definition of a disease management strategy is that there is an optimal set of test(s) whose employment will result in enhanced patient outcome and produce the lowest cost to the health care system. It is critical to identify patients who may be at low risk for major cardiac events, but at high risk for resource utilization (i.e., recurrent angina, hospitalization).

Cost of WISE Tests (including Catheterization, MR, CT, Nuclear, and TMET) and Comparative Costs of Testing (Table 2). Since the WISE protocol uses tests not commonly performed in routine clinical practice (e.g. P-31 myocardial metabolic testing), the test costs listed in Table 4 use charges and adjusted charges (by cost-charge ratio). The cost of care was highest for cardiac catheterization and lowest for treadmill exercise testing. The costs of cardiac SPECT and echocardiography are comparable.

Resource Use and Cost Patterns of Wise Women. Over 7 months of follow-up, overall hospitalization for unstable angina, acute myocardial infarction, or congestive heart failure symptoms was 9.5% (Table 3). The follow-up rates of angiography and coronary revascularization were 5.6% and 12.7%, respectively. As such, for this cohort with only one-third of the women having obstructive coronary disease, a disproportionately high rate of hospitalization and procedure use was documented. Indeed, while 50% of women with non-obstructive coronary disease had fewer or no further angina symptoms at one-year follow-up, an equal 50% of women in this group had persistent symptoms of equal (often daily) frequency and severity compared to baseline.

Table 2. Charges (Median, 25th, and 75th Percentile) and Costs for WISE Tests

Diagnostic Procedures	Charge/Unit Median	25th %ile	75th %ile	Cost/Unit Median	25th %ile	75th %ile
Cardiac Catheterization	$1,690	$1,364	$2,356	$689	$407	$1,065
Magnetic Resonance Imaging	$971	$745	$1,329	$641	$460	$918
CT* of the Chest	$385	(-)	(-)	$85	$31	$108
Cardiac SPECT*	$920	$689	$1,268	$320	$229	$469
Stress Echocardiogram	$366	$284	$457	$284	$224	$291
Treadmill Exercise Test	$291	$214	$357	$79	$44	$119

* CT=Computed Tomography; SPECT=Single Photon Emission Computed Tomography

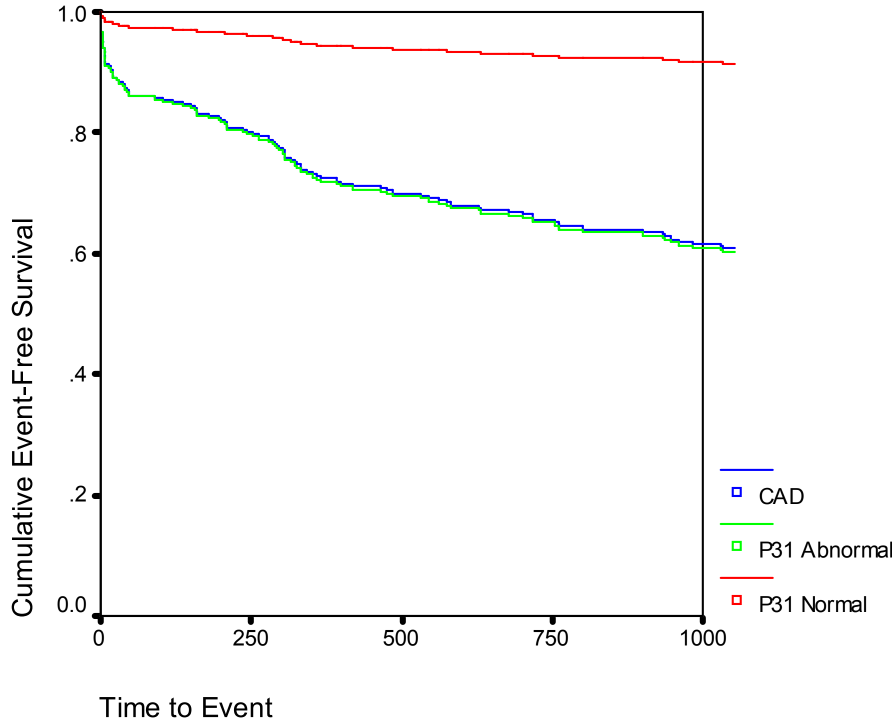
Table 3 summarizes estimated costs of care for WISE women by the extent of angiographic coronary disease. Overall, the intensity of management increased with the overall severity of disease, with higher costs of care for patients with obstructive coronary disease. As a comparison, registry data using the END study group of 3,402 women with stable chest pain (Shaw JACC 1999, Shaw JNC 1999) who underwent a clinically-ordered coronary angiogram were included. Annual costs of care were substantially higher for WISE women as compared to women with stable chest pain in END, suggesting a differential risk or symptom severity that is driving higher resource use patterns in the WISE.

Table 3. Estimated Costs by Extent of Disease in WISE Over 7 Months of Follow-Up as Compared to Women Enrolled in the END* Registry of Stable Chest Pain (3 Year Follow-Up)

	Extent of Disease			
	None n=145	Minimal n=107	Significant n=196	Total N=448
Hospitalization for:				
Unstable Angina	$22,320	$37,200	$178,560	$238,080
MI	(-)	(-)	$22,220	$22,220
CHF	$5,153	$5,153	$36,071	$46,377
Vascular/Stroke	$23,925	$55,825	$79,750	$159,500
Procedures:				
Left Heart Catheterization	$1,691	$6,764	$33,820	$42,275
PTCA	(-)	$51,000	$255,000	$306,000
CABG	(-)	$161,235	$515,952	$677,187
Annual Cost of Care**	$520	$3,469	$7,951	$4,475
END-Observed Cost of Care	$394	$584	$2,203	$1,740

*END = Economics of Noninvasive Diagnosis registry of 3,402 women with stable chest pain (used for comparative purposes only). ** Annual cost of care is estimated from 7 months of follow-up

Updated Results from WISE on the Clinical and Economic Outcomes of P31 MR Spectroscopy. Current clinical and economic outcomes results are available for the use of P31 MR spectroscopy, a measure of metabolic dysfunction. The WISE investigative group reported a reduced PCr/ATP ratio (i.e., $\geq$20%) to be a marker of ischemia (Buchtal NEJM 1999). Recent evidence has suggested that women with an abnormal P31 (n=14) scan have a higher rate of acute coronary syndromes as compared to those with a normal P31 (n=57) study (see Figure below). This figure details risk-adjusted event free survival for women with obstructive coronary disease and normal and abnormal P31 results. Survival free from death, MI, ACS, heart failure, and stroke was 93% for women with a normal P31 study as compared to 64% for women with abnormal P31 findings or known CAD (n=324) (p<0.0001), even after controlling for baseline risk factors, extent of coronary disease, and functional status.



The accrued 3-year costs for these groups of women are detailed in Table 4. Although these results are limited due to small sample sizes, it appears that women with abnormal P31 results are continuing to consume cardiovascular care resources at a substantially higher rate than those with normal P31 results.

Table 4. Accrued 3-year costs

	Costs of Care		
	P31 -	***P31 +***	***CAD***
Initial Diagnosis	$1,717	$1,717	$844
Baseline	$4,016	$4,360	$3,740
Drug at Yr 1	$507	$573	$1,012
Drug at Yr 2	$425	$451	$944
Drug at Yr 3	$267	$433	$609
Anti-Ischemic Rx	$1,732	$2,816	$1,177
Procedure	$223	$762	$7,443
UA / MI	$1,241	$5,586	$4,587
Any Event	$1,514	$5,586	$7,384
Total Cost	***$11,642***	***$22,285***	***$27,739***

Health Policy Implications and Conclusions

Economic considerations in health care are of major importance and play a prominent role in policy decisions both at the local and national level and in the public and private sectors. Increasingly, health care payers have financial limitations requiring the use of critical decisions as to how to allocate ever-limited health care resources (Krumholz et al. BC#33 JACC

2002). The development of cost effectiveness analysis for diagnostic testing in women is an important health care policy question and provides a framework for defining which imaging modalities have the most value to a large proportion of society (Shaw Am J Cardiol 2001, Krumholz et al. 2002). Cost effectiveness analysis does provide a method to evaluate the marginal costs and benefits of alternative atherosclerotic imaging modalities (e.g., lowest cost per life year saved), and clinicians generally value economic evaluations, although they often struggle with implementing their findings into daily clinical practice and into the development of clinical guidelines (Hoffmann Value Health 2002)

A major hurdle for using diagnostic testing in women is that there is very little cost effectiveness evidence upon which to base health care policies. Although, in some imaging areas, we do have population-based epidemiologic trials, we often lack data on the evaluation of test performance in the "real world." When we synthesize the available economic evidence, there are numerous missing critical elements that are needed for the development of high quality cost effectiveness data. Historically, lapses in evidence lead to inefficiencies in the healthcare system and uncontrolled increases in resource utilization. As such, the development of high quality atherosclerotic imaging evidence that defines both clinical and cost effectiveness is critical to the appropriate utilization of current and future technology.

Despite the lack of available evidence on atherosclerotic imaging, diagnostic testing and screening strategies are an accepted strategy in many countries for reducing the burden of other diseases through early detection and intervention (Oortwijn et al., Int J Tech Assess 2001;17:269). Cost effectiveness analysis is a commonplace mechanism to set an array of public policies (Weinstein Value Health 2001). For example, biennial mammography screening is currently recommended for women 40 years of age and older (www.hcfa.gov/quality/3j2-5.htm). The rationale behind mammography screening is that treatment for early stage breast cancer is $11,000 as compared to $140,000 for treatment of late stage cancer. Five-year survival is substantially greater for women whose cancer is detected in the early stages. A similar argument could be considered for diagnostic testing and screening for cardiovascular disease. Expanding cardiovascular risk assessments to include routine diagnostic testing for women could reduce coronary heart disease mortality and improve current primary prevention cost effectiveness estimates (i.e., $5,400 to $44,000 dollars per life year saved, Goldman J Am Coll Cardiol 2001.) Currently, our societal perspective for diagnostic testing does not support routine screening (Rouse Br J Gen Pract 2001). The healthcare payers currently consider that an initial evaluation of cardiac risk factors is sufficient for a cardiovascular risk assessment (in most cases). Given the rising rates of established risk factors, the clinical and economic burden of disease, and the aging of the US population, a comprehensive re-evaluation of research funding and reimbursement should be undertaken. For cardiac imaging, the development and assimilation of new technology should be dependent upon both clinical and cost effectiveness evidence. In the future, cost effectiveness evidence may be used to identify high quality imaging techniques for women and men alike.

4. Current challenges in the areas of communicating messages to health care community, patients and the public

-Limited knowledge base of primary care physicians on strengths and limitations of diagnostic testing in women.

-Recent innovations in diagnostic testing are rarely available in the community setting.

-Cost effectiveness analysis has limited impact on purchasing decisions, reimbursement, and physician test choice.

5. Translating new findings to improved diagnosis and treatment/saving lives.

-Foster development of clinical and economic outcomes – "true effectiveness" data from large health care systems

-Demonstration projects on cost effective diagnostic testing for women

-Gender-based clinical and cost effective guidelines for diagnosis and treatment of at-risk women

6. References

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